Relationships between exercise, smoking habit and mortality in more than 100,000 adults

Short title: Exercise, smoking habit and mortality

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Key words: Physical activity; tobacco products; cardiovascular diseases; cancer.

Abbreviations: Cardiovascular disease (CVD); confidence interval (CI); Health Survey for England (HSE); International Classification of Disease (ICD); metabolic equivalent (MET) Scottish Health Survey (SHS); standard deviation (SD).

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Novelty and impact: This is one of the largest studies of its kind and, given that an outright ban is unlikely, it is important because it suggests that exercise reduces the risks of all-cause, cardiovascular disease, and cancer mortality by around 30% in smokers and ex-smokers.

Abstract

Exercise is associated with reduced risks of all-cause, cardiovascular disease (CVD), and cancer mortality; however, the benefits in smokers and ex-smokers are unclear. The aim of this study was to investigate associations between exercise, smoking habit and mortality. Self-reported exercise and smoking, and all-cause, CVD, and cancer mortality were assessed in 106,341 adults in the Health Survey for England and the Scottish Health Survey. There were 9149 deaths from all causes, 2839 from CVD, and 2634 from cancer during 999,948 person-years of follow-up. Greater amounts of exercise were associated with decreases and greater amounts of smoking were associated with increases in the risks of mortality from all causes, CVD and cancer. These associations were additive, with threefold increases in those who did not exercise and smoked. In the subgroup of 26,768 ex-smokers, the all-cause mortality hazard ratio was 0.70 (95% CI: 0.60, 0.80), the CVD mortality hazard ratio was 0.71 (0.55, 092), and the cancer mortality hazard ratio was 0.66 (0.52, 0.84) in those who exercised compared to those who did not. In the subgroup of 28,440 smokers, the all-cause mortality hazard ratio was 0.69 (0.57, 0.83), the CVD mortality hazard ratio was 0.66 (0.45, 0.96), and the cancer mortality hazard ratio was 0.69 (0.51, 0.94) in those who exercised compared to those who did not. Nicotine is addictive and ex-smokers and those who are unwilling or unable to quit could be encouraged to exercise in order to reduce the risks of all-cause, CVD and cancer mortality by around 30%.

Introduction

Leisure-time physical activity, or exercise, is associated with reduced risks of mortality from all causes, cardiovascular disease (CVD) and cancer.[1] Cigarette smoking is associated with increased risk of mortality from all causes, CVD and cancer.[2, 3] Together, lack of exercise and smoking are among the leading causes of death in the United Kingdom and high-income countries.[4] The prevalence of physical inactivity is around 37% in the United Kingdom, where inactivity is defined as not achieving 150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity per week, or an equivalent combination.[5] The United Kingdom government banned smoking in enclosed public places and in the workplace in July 2007. Since then, the prevalence of smoking in adults in England has fallen from around 25% to around 18%.[6] While much has been done to tackle smoking in the United Kingdom, relatively little has been done to tackle physical inactivity.[7, 8] Physical inactivity costs the UK healthcare system at least INT$1.8 billion per year[9] and policy makers have been urged to take physical inactivity more seriously.[10] Nicotine is a highly addictive substance[11] and around 60% of smokers continue to say that they have not tried to give up in the previous 12 months.[6] In a study of 17,944 middle-aged men followed for 8.5 years, Morris and colleagues[12] reported that coronary heart disease incidence was lower in ex-smokers and smokers who took part in vigorous exercise than in those who did not. An outright ban on smoking might be regarded as an unacceptable loss of freedom in a liberal society;[13] however, governments could promote exercise if there was more evidence of the benefits in ex-smokers and smokers. The objective of this study was to investigate associations between exercise, smoking and all-cause, CVD and cancer mortality using a pooled analysis of eight population-based cohorts in Britain.

Materials and methods

Participants

The Health Survey for England (HSE) and the Scottish Health Survey (SHS) are household-based surveillance studies that are described in detail elsewhere.[14, 15] Participants in the present study were derived from surveys in 1994 (HSE only), 1995 (SHS only), 1998, 1999 (HSE only), 2003, and 2004 (HSE only). The response rates in these surveys were from 66% to 81%, where response rate is defined as the proportion of eligible households that took part. The same organization carried out the surveys using consistent methods.[14, 15] The HSE and SHS samples were selected using a multistage, stratified probability design to be representative of the target populations of the corresponding countries. Stratification was based on geographical areas and not on individual characteristics: postcode (zip code) sectors were selected at the first stage and household addresses selected at the second stage. Local research ethics committees approved all aspects of each survey and all participants gave written informed consent.

Physical activity, exercise and smoking

The questionnaires used to assess physical activity and exercise in the HSE and SHS surveys are described in detail elsewhere.[16, 17] Trained interviewers asked about physical activity and the validity and reliability of the physical activity questionnaires have been reported.[16, 17] The questions were about the frequency (number of days in the last four weeks) and duration (of an average episode) of participation in: domestic physical activity; light-intensity (slow/average pace) and moderate-intensity (fairly brisk/fast pace) walking; and type-specific sports and exercises. For sports and exercises, there was a follow-up question about relative intensity: 'Was the effort of [activity] usually enough to make you out of breath or sweaty?' One metabolic equivalent (MET) is considered to represent resting energy expenditure and activities can be quantified in terms of multiples of resting energy expenditure. For example, brisk walking is defined as 3.8 METs and jogging as 8 METs.[18] We defined exercise as activities of vigorous or very vigorous intensity (energy expenditure rate of ≥6 METs). A MET-hour was computed by multiplying the MET score of an activity by the time (in hours).

We computed total exercise-related energy expenditure (expressed in MET-hours) by summing the MET-hours rate of all activities with energy expenditure rate of ≥6 METs.

Trained interviewers also asked about smoking. Participants were first asked, 'Have you ever smoked a cigarette, a cigar or a pipe?' If participants answered yes, they were then asked, 'Do you smoke cigarettes at all nowadays?' If yes, they were asked, 'About how many cigarettes a day do you usually smoke on weekdays?' And, 'About how many cigarettes a day do you usually smoke at weekends?' Participants who rolled their own cigarettes were asked to estimate tobacco consumption in grams or ounces. The concentration of cotinine in saliva, plasma or urine might best be used to distinguish smokers and non-smokers.[19] Salivary cotinine concentration was measured in 31,007 participants in the HSE (1998, 1999, 2003, 2004) and SHS (1998, 2003) and the Person's correlation between the salivary cotinine concentration and the five self-reported smoking categories was 0.78 ($p<0.001$),[20] a large effect.[21, 22]

Covariates

Health status was assessed by asking participants whether they had 'any longstanding illness, disability of infirmity.' Socioeconomic status assessed using the four group version of the Registrar General's classification: professional and managerial occupations; skilled, non-manual occupations; skilled manual occupations; and, routing and manual occupations.

Mortality follow-up

Participants were flagged by the British National Health Service Central Registry. For participants who survived, the data were censored up to the end of 2009 (Scottish Health Survey) or the first quarter of 2011 (Health Survey for England). Diagnoses for the primary cause of death were based on the *International Classification of Diseases*, Ninth (ICD-9) and Tenth (ICD-10) Revisions. Codes corresponding to cardiovascular disease (CVD) mortality were 390-459 for ICD-9 and I01-I99 for ICD-10. Codes corresponding to cancer mortality were 140-239 for ICD-9 and C00-D48 for ICD-10.

Statistical analysis

The Cox proportional hazards model was used to estimate the single or joint effect of different amounts of exercise and smoking on the risks of all-cause mortality, CVD mortality, and cancer mortality. We compared those who reported no exercise, those who reported less than 60 minutes per week, and those who reported at least 60 minutes per week because adults used to be encouraged to take part in 20-60 minutes of vigorous exercise three or more times per week.[23, 24] In the analyses that were specific to the subgroups of ex-smokers and smokers, we treated exercise participation in a dichotomous fashion to preserve statistical power. We also calculated the associations between total physical activity energy expenditure and all-cause mortality, CVD mortality in ex-smokers and smokers. Domestic activity was not included in the present analysis because of the reported lack of an association between domestic activity and mortality.[25, 26] The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. For the present analyses, calendar time (months) was the timescale. For the present analysis, we excluded those who died during the first 24 months of follow-up. All analyses were adjusted for age, sex, occupational social class, longstanding illness and, where appropriate, mutually for either smoking or exercise. The association between salivary cotinine and mortality was investigated in a sensitivity analysis. All analyses were performed using SPSS version 22 (IBM Inc.).

Results

There were 106,341 participants included in the present study. Seventy-one percent reported no exercise, 12% reported less than 60 minutes per week, and 17% reported at least 60 minutes per week. Table 1 shows participants' characteristics at baseline according to exercise habit. Age was 51±17 years in those who reported no exercise, 37±13 years in those who reported at least 60 minutes per week, and 47±17 years overall. Forty-six percent of participants were male, including 43% of those who reported no exercise and 57% of those who reported at least 60 minutes per week. Forty-eight percent of participants never smoked, including 44% of those who reported no exercise and 58% of those who reported at least 60 minutes per week. Ninety-one percent of participants were of white European ethnic origin. Around a third of participants were employed in professional and managerial occupations. Fifty-six percent of participants reported no longstanding illness, including 51% of those who reported no exercise and 71% of those who reported at least 60 minutes per week. Table S1 in the online supplement shows cotinine levels and smoking habit. Salivary cotinine reflects nicotine exposure in the last 24 hours and, by that definition, misclassification was 3.1% in those categorized as never regular smokers, 9.5% in those categorized as ex-smokers, and 5.4% in those categorized as smokers. Table S2 shows cotinine concentration, age, the proportion in professional and managerial occupations, and exercise habit in smokers.

There were 9149 deaths from all causes, 2839 deaths from CVD, and 2634 deaths from cancer during 999,948 person-years of follow-up (mean±SD: 9.4±4.5 years). Table 2 shows the independent associations of exercise, smoking and mortality. Compared with those who reported no exercise, the hazard ratio for all-cause mortality was 0.72 (95% CI: 0.64, 0.81) in those who reported up to 60 minutes per week of exercise, and 0.69 (95% CI: 0.61, 0.78) in those who reported at least 60 minutes per week of exercise. Greater amounts of exercise were also associated with clear decreases in the risks of mortality from CVD and cancer. Compared with those who reported never smoking, the hazard ratio for all-cause mortality was 1.59 (95% CI: 1.49, 1.74) in those who reported smoking less than 10 cigarettes per day, and 2.86 (95% CI: 2.65, 3.08) in those who reported smoking 20 or more cigarettes per day. Greater amounts of smoking were also associated with clear increases in the risks of mortality from CVD and cancer.

Table 3 shows combined associations of exercise, smoking and mortality. Compared with those who reported at least 60 minutes per week of exercise and never smoking, the all-cause mortality hazard ratio was 1.20 (95% CI: 0.92, 1.57) in those who reported up to 60 minutes per week of exercise and never smoking, and 1.56 (95% CI, 1.28, 1.91) in those who reported no exercise and never smoking. Lower amounts of exercise were associated with clear increases in all-cause mortality risk in ex-smokers and current smokers. Compared with those who reported at least 60 minutes per week of exercise and never smoking, the CVD mortality hazard ratio was 0.90 (95% CI: 0.59, 1.64) in those who reported up to 60 minutes per week of exercise and never smoking, and 2.01 (95% CI: 1.33, 3.06) in those who reported no exercise and never smoking. Lower amounts of exercise were associated with clear increases in CVD mortality risk in ex-smokers and current smokers. Compared with those who reported at least 60 minutes per week of exercise and never smoking, the cancer mortality hazard ratio was 1.73 (95% CI: 1.19, 2.54) in those who reported up to 60 minutes per week of exercise and never smoking, and 1.39 (95% CI: 1.02, 1.90) in those who reported no exercise and never smoking. Lower amounts of exercise were associated with increases in cancer mortality risk in ex-smokers and, particularly, current smokers.

Table 4 shows the association between exercise and mortality in the subgroup of 26,768 ex-smokers, 24% of whom reported taking part in exercise. Compared with ex-smokers who reported no exercise, the all-cause mortality hazard ratio was 0.70 (95% CI: 0.60, 0.80) in ex-smokers who exercised. The associations between exercise and CVD mortality and exercise and cancer mortality were of similar magnitudes. Table 4 also shows the association between total physical activity energy expenditure and mortality in ex-smokers. Greater amounts of physical activity were associated with decreases in the risks of all-cause mortality and CVD mortality. Physical activity energy expenditure per se was not associated with cancer mortality risk.

Table 5 shows the association between exercise and mortality in the subgroup of 28,440 smokers, 24% of whom reported taking part in exercise. Compared with smokers who reported no exercise, the all-cause mortality hazard ratio was 0.69 (95% CI: 0.57, 0.83) in smokers who exercised. The associations between exercise and CVD mortality and exercise and cancer mortality were of similar magnitudes. Table 5 also shows

the association between total physical activity energy expenditure and mortality in ex-smokers. Physical activity was associated with decreases in the risks of all-cause mortality and CVD mortality. Physical activity per se was not associated with decreased risk of cancer mortality.

Selected results are reported in the online supplement. Table S3 shows that the associations between exercise and all-cause mortality were similar across surveys and survey years. Table S3 also shows that the associations between smoking and all-cause mortality were similar across surveys and survey years. Table S4 shows that the combined associations of exercise, smoking and all-cause mortality were similar after further adjustment for body mass index, diabetes and CVD. Table S5 shows the association between salivary cotinine and mortality. Cotinine concentration was associated with increased all-cause mortality risk, increased CVD mortality risk, and increased cancer mortality risk. Table S6 shows the combined associations of exercise, salivary cotinine and all-cause mortality. Compared with those with a salivary cotinine concentration <0.70 $\mu g \cdot ml^{-1}$ who reported at least 60 minutes per week of exercise (the reference group), the all-cause mortality hazard ratio was 1.46 (95% CI: 0.46, 2.75) in those with a salivary concentration of $\geq$15.0 $\mu g \cdot ml^{-1}$ who reported at least 60 minutes per week of exercise, 1.90 (95% CI: 1.05, 3.41) in those with a salivary concentration of $\geq$15.0 $\mu g \cdot ml^{-1}$ who reported up to 60 minutes per week of exercise, and 2.66 (95% CI: 1.90, 3.71) in those with a salivary concentration of $\geq$15.0 $\mu g \cdot ml^{-1}$ who reported no exercise (a salivary cotinine concentration of $\geq$15 $\mu g \cdot ml^{-1}$ is indicative of cigarette smoking in the last 24 hours). Compared with the reference group, the all-cause mortality hazard ratio was 1.42 (95% CI: 1.01, 2.00) in those with a salivary concentration of 0.71-14.99 $\mu g \cdot ml^{-1}$ who reported no exercise (such salivary cotinine concentrations might be indicative of passive smoking). Table S7 shows the associations between exercise, physical activity and mortality in those who reported having never smoked regularly. Exercise was associated with lower all-cause mortality risk, lower CVD mortality risk, and lower cancer mortality risk. Greater amounts of physical activity were associated with decreases in the risks of all-cause mortality and CVD mortality. Physical activity energy expenditure per se was not associated with decreased cancer mortality risk in those who reported having never smoked regularly.

Discussion

The objective of this study was to investigate associations between exercise, smoking and mortality. We found that greater amounts of exercise were associated with decreases and greater amounts of smoking were associated with increases in the risks of mortality from all causes, CVD and cancer. Importantly, we also found that the risks of mortality from all causes, CVD and cancer were reduced by approximately 30% in ex-smokers and smokers who reported taking part in exercise compared to those who did not.

Nicotine is a highly addictive substance and smoking is one of the most prevalent addictions all over the world.[11] Around two thirds of smokers are unwilling or unable to give up[6] and an outright ban is one of the few options left to governments and policy makers in the United Kingdom and elsewhere.[27] An outright ban may not be a realistic option in a liberal society,[13] and the present study is important because it suggests that exercise could be promoted as a way of reducing all-cause, CVD and cancer mortality risks in ex-smokers and smokers. The World Health Organisation recommends that individuals aged 18 to 64 years should do at least 150 minutes per week of moderate-intensity aerobic activity or at least 75 minutes per week of vigorous-intensity aerobic activity.[28] The present study suggests that vigorous-intensity physical activity is particularly important because overall physical activity energy expenditure was not associated with reduced risk of cancer mortality in ex-smokers, smokers, and those who reported having never smoked regularly. Vigorous-intensity exercise increases cardiorespiratory fitness more than the same amount of moderate-intensity exercise[29-31] and low cardiorespiratory fitness may be a stronger predictor of mortality than smoking, obesity and other traditional risk factors.[32, 33] The Nuffield Council on Bioethics 'Intervention Ladder' shows the options available to governments and policy makers, from providing information and enabling choice to guiding choice and restricting choice.[27] Many of the options available to reduce smoking have been successfully implemented.[13] Few of the options available to increase physical activity have been implemented[7, 8] and it is unclear how physical activity might be increased in smokers or the general population.

Morris and colleagues[12] investigated the relationship between vigorous-intensity exercise in leisure-time and coronary heart disease in white-collar workers in the British Civil Service. They observed that age-adjusted

coronary heart disease incidence was 2.1% in ex-smokers who reported taking part in vigorous-intensity exercise and 5.1% in ex-smokers who did not report taking part in vigorous-intensity exercise. Morris and colleagues[12] also observed that age-adjusted coronary heart disease incidence was 4.9% in smokers who reported taking part in vigorous-intensity exercise and 9.7% in smokers who did not report taking part in vigorous-intensity exercise. Li and colleagues[34] searched the literature to 28 February 2015 and included 32 studies in their meta-analysis. Occupational activities, activities of daily living, and leisure-time activities were combined and the pooled relative risk of cancer mortality was 0.80 (95% CI: 0.76-0.85) for the highest versus the lowest physical activity group.[34] The authors did not compare smokers, ex-smokers, and non-smokers in the pooled or subgroup analyses.[34]

To the best of our knowledge, the present study includes one of the largest comparisons of mortality risks in smokers and ex-smokers who do and do not exercise. The only larger study we are aware of is that of Moore and colleagues.[35] Moore and colleagues[35] pooled data from six prospective cohort studies in the United States and observed that the hazard ratio for mortality was 0.75 (95% CI: 0.71-0.79) in smokers and 0.63 (95% CI: 0.61-0.65) in ex-smokers who reported 7.5-14.9 MET-hours per week of leisure-time physical activity compared to those who reported none (here, 7.5 MET-hours per week was equivalent to around 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity). The associations we have observed are biologically plausible. It is well documented that exercise training increases insulin sensitivity, reduces markers of inflammation, reduces blood pressure, improves vascular function, and improves lipids and lipoproteins in the general population.[36] Similar evidence is accumulating in smokers.[37-39] The present study also includes a large number of salivary cotinine concentrations and it is interesting that all-cause mortality risk was higher in passive smokers who reported no exercise.

Our study has some notable strengths and limitations. The main strengths are the large sample size and the assessment of cause-specific mortality. All surveys are susceptible to non-response bias; however, the HSE and SHS samples are weighted in order to be representative of the populations living in private households.[40] Exercise and smoking were only assessed at baseline and we cannot account for any changes in these behaviours over time. Questionnaires and accelerometers can be used to assess physical activity and both

methods have their advantages and disadvantages.[41] It has been suggested that questionnaires remain the mainstay of established surveillance studies.[41] Questionnaires were used in the present surveillance studies and it is noteworthy that questionnaires are particularly advantageous in the assessment of exercise as they help respondents recall vigorous-intensity activities with some accuracy.[42] Accelerometers do not capture cycling and have to be removed during swimming and contact sports.[41] It is perhaps for these reasons that there is poor agreement between questionnaires and accelerometers in surveys.[43] No long-term measure of cigarette smoking was available. Mean cotinine levels were higher in smokers who did not exercise than in smokers who did exercise. While such a difference might suggest that those who did not exercise were heavier smokers than those who did, the present analyses were adjusted for smoking frequency. The Human Development Index (HDI) is a composite index combining indicators of longevity, knowledge and income;[44] however, HDI was not assessed in HSE or SHS. The effect estimates in the present study may have been overestimated or underestimated due to less-than-perfect confounder assessment.[44] We cannot discount the possibility of reverse causation where participants with underlying disease are less likely to exercise; however, we excluded deaths in the first 24 months of follow-up and adjusted for longstanding illness to address the issue of reverse causation.

In conclusion, this large population study suggests that the risks of mortality from all causes, CVD and cancer are reduced by approximately 30% in ex-smokers and smokers who exercise compared to those who do not. Exercise may be a promising way of reducing all-cause, CVD and cancer mortality in ex-smokers and current smokers who are unwilling or unable to quit.

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O'Donovan conceived the study and drafted the paper. Stamatakis acquired and harmonized the dataset. Hamer carried out the statistical analysis, had full access to the data, and takes responsibility for the integrity and accuracy of the results. All authors contributed intellectually to refine the study design. All authors contributed to the critical revision of the manuscript. O'Donovan and Hamer acknowledge support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC – EM), Leicester Clinical Trials Unit, and the NIHR Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit, which is a partnership between University Hospitals of Leicester NHS Trust, Loughborough University and the University of Leicester. Stamatakis is funded by the National Health and Medical Research Council (NHMRC) through a Senior Research Fellowship. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health, or the NHMRC.

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Table 1. Participants' characteristics at baseline (n=106,341)

Variable	Exercise		
	None	<60 min·wk^{-1}	≥60 min·wk^{-1}
Age, years	51±17	39±14	37±13
Male, %	43	45	57
Cigarette smoking status			
Never regular smoker, %	44	54	58
Ex-smoker, %	27	22	21
<10 per day, %	7	9	9
10 to 19 per day, %	12	10	8
≥20 per day, %	10	5	4
Ethnicity			
White European, %	90	91	90
Other, %	10	9	10
Occupation			
Professional, %	4	7	8
Managerial, %	25	34	34
Skilled, non manual/manual, %	44	42	39
Semi-skilled, manual, %	20	14	14
Unskilled, manual, %	7	4	4
Other, %	0.4	0.4	0.9
Had longstanding illness, %	49	35	29

Table 2. Cox proportional hazard ratios (HR) for independent associations between exercise, smoking and mortality (n=106,337)*

	N	All-cause mortality HR (95% CI), 9,149 events	CVD mortality HR (95% CI), 2,839 events	Cancer mortality HR (95% CI), 2,634 events
Exercise				
None	75795	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
<60 min·wk^{-1}	12611	0.72 (0.64, 0.81)	0.66 (0.53, 084)	0.85 (0.72, 1.02)
≥60 min·wk^{-1}	17935	0.69 (0.61, 0.78)	0.58 (0.44, 0.75)	0.70 (0.57, 0.86)
P, trend		<0.001	<0.001	<0.001
Cigarette smoking				
Never regular smoker	51133	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Ex-smoker	26768	1.26 (1.20, 1.33)	1.11 (1.02, 1.21)	1.34 (1.22, 1.48)
<10 per day	7802	1.59 (1.49, 1.74)	1.27 (1.06, 1.51)	1.54 (1.29, 1.83)
10 to 19 per day	11459	2.10 (1.95, 2.27)	1.96 (1.71, 2.26)	2.12 (1.85, 2.43)
≥20 per day	9179	2.86 (2.65, 3.08)	2.33 (2.02, 2.68)	3.09 (2.72, 3.52)
P, trend		<0.001	<0.001	<0.001

*Models adjusted for age, sex, occupation, longstanding illness and mutually for either smoking or exercise. Participants who died during the first 24 months of follow-up were excluded.

Table 3. Cox proportional hazard ratios (HR) for combinations of exercise and smoking in relation to mortality (n=106,337)*

Smoking	Exercise		
	≥60 min·wk^{-1}	<60 min·wk^{-1}	None
All-cause mortality HR (95% CI), 9149 events			
Never smoked	1.00 (Reference)	1.20 (0.92, 1.57)	1.56 (1.28, 1.91)
Ex-smoker	1.37 (1.04, 1.80)	1.30 (1.00, 1.70)	1.96 (1.61, 2.40)
Current smoker	2.27 (1.64, 2.18)	2.35 (1.74, 3.19)	3.38 (2.76, 4.13)
CVD mortality HR (95% CI), 2839 events			
Never smoked	1.00 (Reference)	0.90 (0.49, 1.64)	2.01 (1.33, 3.06)
Ex-smoker	1.23 (0.69, 2.19)	1.81 (1.08, 3.02)	2.19 (1.44, 3.32)
Current smoker	2.58 (1.33, 5.03)	2.45 (1.30, 4.64)	3.64 (2.40, 5.53)
Cancer mortality HR (95% CI), 2634 events			
Never smoked	1.00 (Reference)	1.73 (1.19, 2.54)	1.39 (1.02, 1.90)
Ex-smoker	1.57 (1.03, 2.39)	1.19 (0.76, 1.85)	1.93 (1.41, 2.63)
Current smoker	1.51 (0.88, 2.59)	1.96 (1.21, 3.18)	3.32 (2.44, 4.51)

*Models adjusted for age, sex, occupation and longstanding illness. Participants who died during the first 24 months of follow-up were excluded.

Table 4. Cox proportional hazard ratios (HR) for exercise, physical activity and mortality in ex-smokers (n=26,768)*

	N	All-cause mortality HR (95% CI), 3629 events	CVD mortality HR (95% CI), 1138 events	Cancer mortality HR (95% CI), 989 events
Exercise				
No	20287	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Yes	6481	0.70 (0.60, 0.80)	0.71 (0.55, 0.92)	0.66 (0.52, 0.84)
Physical activity tertile				
Lower, <6.62 MET-hr·wk^{-1}	9566	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Middle, 6.63-23.8 MET-hr·wk^{-1}	8677	0.70 (0.65, 0.76)	0.69 (0.60, 0.79)	0.95 (0.82, 1.11)
Upper, >23.8 MET-hr·wk^{-1}	8520	0.61 (0.55, 0.67)	0.55 (0.46, 0.66)	0.91 (0.77, 1.07)
P, trend		<0.001	<0.001	0.52

*Models adjusted for age, sex, occupation and longstanding illness. Participants who died during the first 24 months of follow-up were excluded.

Table 5. Cox proportional hazard ratios (HR) for exercise, physical activity and mortality in smokers (n=28,440)*

	N	All-cause mortality HR (95% CI), 2476 events	CVD mortality HR (95% CI), 673 events	Cancer mortality HR (95% CI), 807 events
Exercise				
No	21579	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Yes	6861	0.69 (0.57, 0.83)	0.66 (0.45, 0.96)	0.69 (0.51, 0.94)
Physical activity tertile				
Lower, <6.62 MET-hr·wk^{-1}	9793	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Middle, 6.63-23.8 MET-hr·wk^{-1}	9340	0.75 (0.68, 0.83)	0.80 (0.66, 0.97)	0.87 (0.73, 1.03)
Upper, >23.8 MET-hr·wk^{-1}	9300	0.78 (0.70, 0.86)	0.79 (0.64, 0.97)	0.97 (0.81, 1.16)
P, trend		0.001	0.061	0.99

*Models adjusted for age, sex, occupation, longstanding illness, and smoking volume (<10 per day, 10-19 per day, ≥20 per day). Participants who died during the first 24 months of follow-up were excluded.